Tolerability of levonorgestrel emergency contraception in adolescents

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KEY WORDS
Tolerability
Side effects
Emergency contraception
Adolescents

Objective: We evaluated the tolerability of emergency contraception in adolescents.
Study design: In this descriptive study, 10.75 mg levonorgestrel tablet was administered to 52 females aged 13-16 with instructions to take the second tablet 12 hours later (unprotected intercourse was not an entry requirement). Participants kept diaries of side effects and menstrual patterns. We assessed correct use, side effects caused by treatment, and impact on menstrual cycle.
Results: Virtually all participants used the drug correctly, with no serious adverse events. Minor expected side effects occurred, including nausea, fatigue, and vomiting. There was no difference in reporting of side effects by age. Adolescents’ mean duration of menses was comparable pre- and post-treatment (5.3 vs 5.0 days; P = .146), and onset of menses was within the expected range. Ninety percent of participants reported they would recommend emergency contraception to a friend or relative if needed.
Conclusion: Adolescents tolerated the medication well, experiencing transient side effects.
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In 1999, the United States Food and Drug Administration (FDA) approved 0.75 mg levonorgestrel Plan B® (Gedeon Richter, Ltd, Budapest, Hungary) tablets for use postcoitally as an emergency contraceptive. The safety and efficacy of emergency contraception (EC) is well established for adults. In the World Health Organization (WHO) Task Force study of levonorgestrel EC, 89% of expected pregnancies were prevented with correct use of the treatment.1 Moreover, levonorgestrel was found to have an acceptable side effect profile, with 23% of participants reporting nausea and 5.6% vomiting, lower levels than with the standard Yuzpe regimen (ethinylestradiol 100 µg plus levonorgestrel 0.5 mg or dl-norgestrel 1.0 mg, repeated 12 hours later). Subsequent studies of women in various countries also showed levonorgestrel EC to be well tolerated.2-4

While young age is associated with greater awareness of emergency contraception, use of the method is more common among adult women than adolescents.5,6 We have scant data on the tolerability and acceptability of the method to adolescents. As with other hormonal
contraceptives, current FDA labeling of Plan B<sup>®</sup> is not specific with respect to use in girls aged 16 years and younger. If the FDA moves to switch Plan B<sup>®</sup> emergency contraception to over-the-counter status, adolescents as well as adults will be able to use it without provider supervision. Clinical trials of contraceptives in the US include adults only, a minority of whom are between the ages of 18 and 19 years. While enrolling adolescents in clinical trials is difficult, there is a growing recognition of the need to address the paucity of data in pediatric subpopulations.<sup>7,8</sup>

One study on levonorgestrel implants showed that tolerance of side effects was comparable among adolescents and adults.<sup>9</sup> Studies of low-dose progestin-only pills for long-term contraception have shown no differences in safety or efficacy among adolescents aged 16 years and older compared with adults.<sup>10</sup> However, there is no information on the higher doses of progestins used in emergency contraception.

The primary objective of this study was to evaluate the tolerability of levonorgestrel emergency contraception (Plan B<sup>®</sup>) in adolescent females. Specifically, the study aimed to characterize the side effects profile, assess correct use of the method, and ascertain the impact on the menstrual cycle in a sample of young adolescents.

**Material and methods**

**Study design**

This study was a single-center, open-label observational trial. Two 0.75 mg Plan B<sup>®</sup> levonorgestrel tablets were administered orally to adolescent females recruited at a publically funded San Francisco family planning clinic and through flyers at community centers. Inclusion criteria for the study were: females aged 12 to 16 years who had reached menarche; good health based on physical examination, medical history, urine analysis, and laboratory evaluation; normal menstrual cycles for the previous 6 cycles, varying in length from 21 to 35 days; no unprotected intercourse during the current cycle (to avoid very early pregnancy); willing to abstain from intercourse or to use condoms for the study duration; no sex steroid use (including hormonal contraception) in the past 2 months. Exclusion criteria were pregnancy or breastfeeding, hypersensitivity to levonorgestrel or other progestins, use of an investigational drug within 30 days, history of emotional or psychiatric disorders or use of psychotropic agents, evidence or admission of illicit drug or alcohol abuse. Research assistants told potential participants and their parents that the study was looking at emergency contraception and side effects and menstrual bleeding in girls aged 12 to 16 years. Parental consent was required for participation. The study was approved by the University of California, San Francisco, Committee on Human Research. Procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki of 1975, revised in 1983.

Research assistants administered study procedures at the clinic site. Participants were given the first dose of emergency contraception in the clinic, and were instructed to take the second dose in 12 hours. They were given diary cards and were asked to record the date and time of the second dose, and to keep a daily record of any bleeding and side effects until the follow-up visit 3 weeks after enrollment. The diary was collected at the follow-up visit. The format of the diary card, as well as the methods, including product, dose, and route of administration were as similar as possible to those in the levonorgestrel arm of the large WHO multicenter trial<sup>11</sup> that evaluated side effects. Unlike the WHO trial, which compared the efficacy and safety of different emergency contraceptive agents and regimens, this trial examined only the current FDA-approved Plan B regimen of 2 doses 12 hours apart. The participants in this study had not experienced unprotected intercourse during the present cycle, while the participants in the WHO trial were seeking emergency contraception because of need after an act of unprotected intercourse.

Participants who had not resumed menses at follow-up returned for an additional visit. The study period was thus from 3 to 5 weeks, depending on regular menstrual cycle variation and timing of menses subsequent to dosing. Research assistants took medical histories at enrollment, and administered short interviews at enrollment and follow-up that included items on the participant’s experience using emergency contraception. Participants were given $50 at enrollment and $50 at follow-up; if required to return for a second follow-up visit, participants were given an additional $50.

**Measures**

Correct use of the medication was measured by self-reports of whether participants followed instructions to ingest the second dose, and whether they had any problems following directions. We used diary data to measure the frequency (in days) of side effects, including nausea, vomiting, headache, dizziness, fatigue, breast tenderness, lower abdominal pain, and diarrhea. To assess impact on menses, we measured the length of menses before and after treatment (ie, mean duration of menstrual flow), and also measured the time until menses after administration of the treatment compared with the anticipated date (calculated from date of last menstrual period and cycle length). As a general acceptability measure, we also recorded whether participants would recommend emergency contraception to a friend or relative if needed (yes, no, not sure).
Analysis

To analyze side effects caused by treatment, we compared side effects reported by participants during the first week (days 1 to 7) after drug administration to those reported during the second week (days 8 to 14), when virtually no levonorgestrel was present in the serum; a pharmacokinetic study showed the mean half life of levonorgestrel in adolescents to be 21 hours.  

We used two-sided \( t \) tests to compare the number of daily reports of each side effect during the first week (days 1 to 7) with the number of daily reports of the same side effect during the second week (days 8 to 14). We used two-sided \( t \) tests to assess any difference in menstrual flow caused by treatment: menstrual flow at last menstrual period (LMP) before enrollment was compared with menstrual flow after treatment. Kruskal-Wallis tests were used to detect age differences in return to menses within the adolescent sample, as well as any differences in correct use, side effects, or acceptability. Significance is reported at the .05 level. Stata 6.0 (College Station, Tex) was used for the analysis.

Results

A total of 60 participants were enrolled in the study. Six participants enrolled were ineligible; 1 was younger than 12 years old (11.6 years), and 5 had taken levonorgestrel within 2 months of recruitment. Two participants, aged 16 years, were lost to follow-up. We analyzed data from the 52 eligible participants who completed the study. Summary baseline characteristics are presented in Table I. Participants ranged in age from 13 to 16 years, with a mean age of 15.5 years. Most participants were racial/ethnic minorities; 61% were African American, 19% Latina, 15% multiracial, and 4% white.

Correct use

Ninety-eight percent of participants (51/52) reported taking the second dose of Plan B\(^\text{®} \) as instructed. Ninety-four percent (49/52) reported no problems in following directions. Because correct use was uniformly high, we could not test variation in correct use by age.

Side effects

In Table II, we compared symptoms reported during the first week (days 1 to 7) with symptoms reported during the second week (days 8 to 14). Nausea was reported in the first week by 38.5% of participants and vomiting by 11.5%. Several other side effects were also commonly reported. Reports of some symptoms, including nausea (\( P = .001 \)), fatigue (\( P = .002 \)), headache (\( P = .004 \)), and diarrhea (\( P = .004 \)) were significantly higher during the first week. However, for others, reports were not significantly higher in the first week than they were in the second, including vomiting (\( P = .160 \)), dizziness (\( P = .130 \)), breast tenderness (\( P = .582 \)), and lower abdominal pain (\( P = .088 \)). Kruskal-Wallis tests showed no difference by age in any of the reported side effects (Table III).

Impact on menses

There was no difference in the mean duration of menses for the adolescents before and after treatment (Table IV). In the last menstrual period before enrollment, the mean duration of menses was 5.0 days, and after treatment the mean duration of menses was 5.3 days (\( P = .146 \)). Eight percent experienced a delay in return to menses over 7 days, 62.5% had a return to menses within 7 days of the anticipated date, and 29% an early onset of more than 7 days. Kruskal-Wallis tests showed no differences by age in return to menses (\( P = .104 \)) or in duration of flow compared with normal (\( P = .313 \)). One participant had unprotected intercourse and had an intrauterine pregnancy.

Recommendation of emergency contraception

Ninety percent (47/52) of participants reported that they would recommend emergency contraception to a friend or relative if needed. All others responded that they were not sure. Kruskal-Wallis tests showed no difference by age (\( P = 0.756 \)) in whether a participant would recommend EC or was unsure about it. There were no serious adverse events.
Concerns about the side effects of hormonal contraception are common among the general public.12,13 Beliefs about negative side effects, even when false, can stop adolescents from using hormonal contraception.14 However, this age group stands to benefit the most from use of the product, and to lose the most from misconceptions because almost 80% of adolescent pregnancies are unintended.15 This study found that adolescents reported minor and transient side effects, similar to those reported in previous adult trials, including nausea and vomiting. However, the adolescents tended to report many symptoms even when they no longer had levonorgestrel in their serum. For nausea or headaches, common and somewhat subjective symptoms, there were significantly higher reports during the first week, but for vomiting, the least subjective symptom, there were no significant differences in levels reported. Vomiting is an important symptom because of its potential impact on efficacy.

A comparison between the side effects reported in this study with the data from adults in the large international WHO trial1 also shows little difference in the levels of vomiting reported. Some of the side effects, such as nausea, headaches, and fatigue are reported at higher levels by this adolescent sample, while others, including abdominal pain and breast tenderness, are at similar levels. However, comparisons should be interpreted with caution because of many differences in the samples other than age, including need for emergency contraception at enrollment and different nationalities and racial/ethnic compositions. International studies on emergency contraception as well as other medications have shown that women of different nationalities and races/ethnicities experience and report symptoms differently.3,16-18 There is some evidence that women in developed countries report more side effects than women in developing countries.4 However, all reported side effects were well within the range of what adult trials have shown and present no serious health risks. A randomized, controlled placebo trial would be necessary to

**Table II** Diary reports of symptoms by week (n = 52)

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Week 1 (days 1 to 7)</th>
<th>Week 2 (days 8 to 14)*</th>
<th>t test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>20 38.5 (25.3-53.0)</td>
<td>7 13.5 (5.6-25.8)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 11.5 (3.6-23.4)</td>
<td>2 3.9 (0.5-13.2)</td>
<td>.160</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 26.9 (15.6-64.0)</td>
<td>6 11.5 (4.4-23.4)</td>
<td>.130</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 40.4 (27.0-54.9)</td>
<td>10 19.2 (9.6-32.5)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26 50.0 (35.8-64.1)</td>
<td>17 32.7 (20.3-47.1)</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>7 13.5 (5.9-25.8)</td>
<td>5 9.6 (3.2-21.0)</td>
<td>.582</td>
<td></td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>13 25.0 (14.0-38.9)</td>
<td>9 17.3 (8.2-30.3)</td>
<td>.088</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 15.4 (6.9-28.1)</td>
<td>4 7.7 (2.1-18.5)</td>
<td>.004</td>
<td></td>
</tr>
</tbody>
</table>

* Symptoms in days 8 to 14 when levonorgestrel no longer biologically available.
1 Paired t test comparing number of days symptom reported in weeks 1 and 2.
2 P ≤ .010.

**Table III** Differences in reports of symptoms (days 1 to 7) by age (n = 52)

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Kruskal-Wallace test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3.329 (1)</td>
<td>.068</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.313 (1)</td>
<td>.252</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.824 (1)</td>
<td>.364</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.959 (1)</td>
<td>.327</td>
</tr>
<tr>
<td>Headache</td>
<td>0.010 (1)</td>
<td>.920</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>0.604 (1)</td>
<td>.437</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>0.070 (1)</td>
<td>.792</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.017 (1)</td>
<td>.155</td>
</tr>
</tbody>
</table>

**Table IV** Return to menses* among adolescents

<table>
<thead>
<tr>
<th>Mean (± SD)</th>
<th>Mean duration of flow (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMP at admission (n = 52)</td>
<td>5.0 (± 1.1)</td>
</tr>
<tr>
<td>LMP at follow-up (n = 46)</td>
<td>5.3 (± 1.1)</td>
</tr>
<tr>
<td>Amount of flow (n = 45), at follow-up, compared with normal</td>
<td>n (%)</td>
</tr>
<tr>
<td>Similar</td>
<td>25 (55.6%)</td>
</tr>
<tr>
<td>Less</td>
<td>9 (20.0%)</td>
</tr>
<tr>
<td>More</td>
<td>11 (24.4%)</td>
</tr>
</tbody>
</table>

Timing of initiation of menses (n = 48), LMP at follow-up, as compared with expected | n (%) |
| Within 7 days                | 30 (62.5%)                |
| > 7 days earlier             | 14 (29.2%)                |
| > 7 days later               | 4 (8.3%)                 |

* Numbers vary because of the following: 2 participants did not begin menses by follow-up visit; 1 became pregnant during study; 2 were still bleeding at follow-up visit; 1 had missing data on menses.
clarify any differences in adolescent users and adults. Adolescents seeking emergency contraception should be aware, as should adults, that the medication may cause certain uncomfortable, but transient side effects.

A possible concern with adolescents is that they may be more vulnerable to menstrual disturbances compared with adults, but our study did not demonstrate greater disturbances. The variation in return to menses was within the range expected from adult trials, and the mean duration of menses was not affected by treatment. Recent research has shown that the earlier in the cycle that emergency contraception is taken, the more likely that return to menses will be early, although EC taken later in the cycle does not appear to delay the return to menses. A delay in return to menses, rather than early onset, would be of greatest concern to an adolescent waiting to find out if she were pregnant; in this study, only a small proportion had a delay in return to menses. Regular menses for at least 6 cycles before study enrollment was an eligibility criteria for the study, so it is possible that adolescents with anovulatory cycles who have irregular periods may demonstrate greater disturbances after administration of emergency contraception. All women should be counseled that they might experience menstrual disturbances after using emergency contraception, and to seek pregnancy testing for delayed menses.

A small but growing body of research has examined access and use of emergency contraception among adolescents, but data on acceptability are scarce. Based on a general measure of whether they would recommend the method to others if needed, these data showed a high level of acceptability for emergency contraception among young adolescents. Future studies on additional aspects of acceptability are needed to understand more fully adolescent user perspectives on the method.

This study adds to this growing body of evidence to show that adolescents in particular tolerate the medication well and appear to be able to use it correctly. Adolescents were capable of following simple instructions for correct use of this medication and suffered no serious adverse events. Recent studies have shown high efficacy of emergency contraception when both tablets are taken together at the same time as a single dose of 1.5 mg of levonorgestrel, and this change will make it even easier to follow directions for use. If levonorgestrel emergency contraception is switched to over-the-counter status, use should not be restricted to adults because of concerns about unknown side effects in adolescents. Similar to adults, adolescents should not experience serious side effects in using this medication.

Acknowledgments

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References
